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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,219	03/11/2004	Matilde Bustos De Abajo	U 015070-8	3487

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,219	ABAJO ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-18 and 28-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-18 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/7/08 has been entered. Applicant's amendment, response, and declaration under 37 CFR 1.132 received on 3/7/08 have been entered. Claims 1-11 and 19-27 are canceled, and new claims 28-33 have been added. Claims 12-18 and 28-33 are pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Objections

Claim 32 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 32 depends upon itself. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form. It is suggested that claims 32 be amended to depend on claim 31.

Claim Rejections - 35 USC § 112

The rejection of claims 12-19 under 35 U.S.C. 112, first paragraph, for lack of enablement, is withdrawn over canceled claim 19 and maintained in modified form over amended and new claims 12-18 and 28-33. Applicant's amendments, arguments, and the declaration under 37 CFR 1.132 by Jesus Prieto Valtuena have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that a consideration of the Wands factors in combination with the submitted Declaration under 35 CFR 1.132 shows that the specification enables the practice of the invention as now claimed without undue experimentation. According to applicant, the Declaration of Dr. Valtuena shows that the skilled artisan could have routinely practiced the method as claimed without undue experimentation based on the guidance provided by the specification and the knowledge available in the prior art. The applicant also argues that evidence in the form of two post-filing publications demonstrates that the applicants were able to reproduce the hepatoregenerative effects obtained with Ad-CT-1 by administering recombinant CT-1 using previously known techniques available prior the instant effective filing date. The applicant further argues that safety considerations are not relevant to the analysis of enablement and that the claims are not drawn to treatment of life-threatening diseases but rather to methods for protecting the liver of a subject about to undergo liver surgery or for stimulating hepatic regeneration in a subject who has experienced loss of functional liver cells irrespective of whether the protection or regeneration results in any treatment of any disease.

In response, the Declaration by Dr. Valtuena has been fully and respectfully considered, along with the accompanying publication evidence, but has not been found persuasive in demonstrating enablement for the full scope of the amended claims as written. The Declaration states that publications in the prior art provide guidance for therapeutic dosages of CT-1 polypeptide, citing Jin et al. (1995) and WO95/29237. While Jin et al. is of record, it is noted that WO95/29237 is not of record and has not been provided to the examiner for consideration. Jin et al. (1995) teaches to administer CT-1 intraperitoneally to mice at a dosage of 0.5 or 2ug twice daily for 14 days, which the declaration states corresponds to approximately 40-160 ug/kg/day. However, the declaration states that the results reported by Jin et al. do not indicate that this dosage resulted in hepatoregeneration. The declaration then states that the WO95/29237 publication teaches the administration of between 10 ug/kg/day to 10 mg/kg/day. However, as indicated, this reference has not been provided for consideration by the examiner or made of record. The post-filing evidence discussed in the Declaration and provided as an exhibit for examiner's consideration is Iniguiz et al. (2006). This reference teaches that intravenous administration of 200 ug/kg, 400 ug/kg, or 800 ug/kg of CT-1 could protect rats from ischemic liver damage, including necrosis, caused by brief periods of ischemia. However, nothing in this reference teaches or suggests that the administration of CT-1 induces hepatoregeneration in a damaged liver, such as a resected liver, a liver following transplant, or one damaged by chronic or acute hepatitis or cirrhosis. It is further noted that liver damage caused by hepatitis, cirrhosis or liver transplant is substantially different from a brief period of ischemia. As such, while the post-filing data indicates that administration of CT-1 polypeptide can protect against liver

damage caused by brief periods of ischemia, the data is not commensurate in scope with the claims methods and does not provide any evidence for hepatoregeneration.

The declaration further states that the results reported in Iniguiz et al. reproduces the hepatoregenerative effects observed with adenovirus CT-1 presented in the specification. However, this is not agreed. As noted in the previous action, the working examples all utilize the administration of a recombinant replication defective adenoviral vector encoding CT-1(Ad-CT-1). While the working examples do demonstrate that intravenous administration of Ad-CT-1 to various models can prevent liver damage through inhibition of apoptosis/necrosis caused by ConA, D-Gal and TNF alpha, or anti-Fas antibody, and also protect against apoptosis/necrosis in remaining liver tissue following subtotal liver resection, nothing in the working examples demonstrates that the CT-1 expressed by the adenovirus stimulated hepatic regeneration after either subtotal hepatectomy or the administration of liver damaging agents.

In addition, while applicant now argues that the methods as claimed do not require the treatment of life-threatening diseases such as alcoholic hepatitis, this is not agreed. Amended claim 12 clearly recites a method for treating a subject whose liver has experienced loss of functional liver cells. Claims 15-17 depend on claim 12 and clearly recite that the subject has a chronic liver disease, hepatitis, or cirrhosis. Thus, the claims under examination clearly encompass treatment of these diseases.

It is further noted that the previous office actions analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific

reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. Further, case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). In addition, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Also, applicant is reminded that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. In particular, the previous office actions discussed that the prior art at the time of filing teaches that alcoholic hepatitis and cirrhosis are life-threatening diseases for which few treatments are currently available. Narayanon Melon et al. was cited for teaching that while the stimulation of liver regeneration represents a future potential treatment approach for hepatitis and cirrhosis, Narayanon Melon et al. teaches that, "[t]his concept has been examined in patients with alcoholic hepatitis by treatment with insulin and glucagon, which is thought to stimulate liver regeneration. However, the results have been discouraging.", and that "[t]herapies using more selective hepatotrophic agents, such as hepatocyte growth factor, are compelling but remain untested.." (Narayanon Melon et al. (2001) Mayo Clinic Proceedings, Vol. 76 (10), 1021-1029, see page 1027). It is noted that CT-1 is not hepatoselective as it effects many organs and cells. Thus, the prior art at the time of filing establishes that therapy of chronic liver diseases such as alcoholic hepatitis and cirrhosis by stimulating liver regeneration was considered unpredictable. Applicant's disclosure does not overcome the art recognized unpredictability for treating these

diseases by stimulating liver regeneration as the specification does not provide any specifics as to protein dosage or administration or provide any evidence for therapeutic liver regeneration in patients with hepatitis or cirrhosis. Applicant's previous arguments that the animal models tested in the working examples are art-recognized models of hepatitis and liver injury caused by chronic alcohol consumption also does not overcome the art-recognized unpredictability of stimulating hepatic regeneration in patients with these diseases as the working examples do not utilize CT-1 polypeptide administration and do not in fact demonstrate any level of hepatic regeneration induced by Ad-CT-1 in any of the models used. Also, as discussed above, the declaratory evidence does not overcome these issues as the data provided by Iniguiz et al. does not demonstrate hepatic regeneration following CT-1 administration or any treatment effect on any chronic liver disease.

Therefore, based on the state of art for stimulating hepatic regeneration, particularly for treating diseases such as hepatitis and cirrhosis, the limited disclosure in the specification, no more than a single sentence regarding CT-1 polypeptide administration, for using CT-1 polypeptide to protect against liver damage or treat liver disease by hepatic regeneration, the limitations of the working examples to the use of adenoviral CT-1 and the lack of evidence for hepatic regeneration, and the breadth of the claims, it would have required undue experimentation to practice the full scope of the claims as written. However, based on the evidence of record, including the newly submitted declaratory evidence, the following scope of enablement has been identified: the specification provides an enabling disclosure for methods of protecting liver cells from damage caused by brief periods of ischemia comprising administering an effective amount of CT-1 polypeptide to liver cells prior to or during the ischemic period.

Therefore, for reasons of record as discussed in detail above and in previous office actions, the rejection of claims 12-18 and 28-33 stands.

Claim Rejections - 35 USC § 102

The rejection of claims 12 and 14 under 35 U.S.C. 102(b) as being anticipated by Jin et al. (1996) Cytokine, Vol. 8 (12) 920-926, is withdrawn over claims 12 and 14 in view of applicant's amendments and arguments. Specifically, independent claims 12 and 14 have been amended to recite that the subject to which CT-1 is to be administered is either a subject whose liver has experienced a loss of functional liver cells or a subject in need of or subject to hepatectomy or liver transplant. While Jin et al. teaches the administration of CT-1 and shows that liver size increased following administration, the subjects in Jin et al. were normal mice. Jin et al. does not teach or suggest administering CT-1 to subjects with damaged livers or to subjects requiring or having had a hepatectomy or liver transplant.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology

center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633